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Editorial comment

Coronary artery bypass, percutaneous coronary intervention, and mortality: a reflection on methods

Cirugía, intervencionismo coronario y mortalidad: algunos aspectos metodológicos

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Revista Española de Cardiología recently published a systematic review and meta-analysis by Formica et al.[1] The main objective of the work was to compare the effectiveness of surgical revascularization and percutaneous coronary intervention (PCI) in reducing very long-term mortality (> 5 years) in patients with left main coronary artery lesions or with complex multivessel disease.

In systematic reviews, the original primary research studies are the unit of analysis.[2] This type of design allows synthesis of the available scientific information and usually uses a meta-analysis to obtain a weighted estimate of the effect of an intervention or the magnitude of an association between an exposure and an event of interest.

The article by Formica et al.[1] is highly interesting from both a clinical and methodological perspective. In this editorial, we provide some reflections of a methodological nature, some general and others more specific, regarding this systematic review.

Registry of systematic reviews. As in clinical trials, there is a specific registry for systematic reviews called PROSPERO.[3] The registry aims to avoid duplication of effort and ensure transparency by reducing the risk of bias. The review by Formica et al. is registered in PROSPERO,[1] and the objectives and methods declared in the article are in line with the authors' original statements.

Adherence to PRISMA recommendations. The authors followed PRISMA recommendations for the presentation of the objectives, methods, results, and conclusions of systematic reviews.[4] Such recommendations include a clear definition of the information sources and search criteria used to identify studies relevant to the question posed, as well as a detailed presentation of the results of this search.

Analysis of the risk of bias. A risk of bias analysis is performed of the studies included in the meta-analysis. Because biases can call into question and even potentially invalidate the conclusions of a study, this analysis is crucial in systematic reviews. Formica et al. used a recognized instrument for clinical trials, the RoB 2 [5]; for observational studies, the recommended instrument is the ROBINS-E.[6]

Meta-analysis with fixed- or random-effects models. Meta-analyses use either fixed- or random-effects models.[7] Fixed-effects models assume a constant magnitude of the effect of the intervention or association across studies and attribute possible differences to chance and sample size. In contrast, random-effects models allow for variations in effect size among studies due to differences in participant characteristics, intervention type, or other uncontrolled variables.

To assess heterogeneity among studies, the I^2 heterogeneity index is used. In the study by Formica et al., the I^2 in the main event analysis was 14.37%, indicating that 85.63% of the between-study variability was attributable to chance. Notably, in practical terms, random-effects models assign greater weight to small studies and result in a wider confidence interval of the meta-analysis estimator, making them a more conservative approach.[7]

Digitization of Kaplan-Meier curves. To obtain individual data for the participants in each study, the authors digitized the Kaplan-Meier curves. This approach allowed them to calculate the mortality incidence density (incidence rate) at each follow-up point.[8]

Discussion of Kaplan-Meier curves and heterogeneity control. Importantly, Kaplan-Meier curves report the speed at which the event of interest occurs in each study, without considering possible differences in participant characteristics that could influence the results. To address this possible heterogeneity, the authors incorporated a frailty term in their analysis.[9] The theta frailty statistic quantifies the variability explained by this term, which, in this study, was small (0.08 or 8%).

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Comparative analysis via Cox regression. To compare the mortality incidence density between the 2 evaluated interventions, the authors used Cox regression, assuming proportional hazards during the follow-up period analyzed. To analyze this proportionality, various graphical approaches are used, such as analysis of Kaplan-Meier curves, log(–log) survival curves (a transformation of the estimated survival curves in the groups), the ratio of predicted to observed events, and Schoenfeld residuals. In most of these graphical methods, risk proportionality can be assumed. In addition, the formal analysis concludes that the null hypothesis of risk proportionality cannot be ruled out, meaning that it can also be assumed.

Analysis of long- and very long-term mortality. To analyze long- and very long-term mortality, the authors used 2 additional methodological approaches: *a)* a landmark analysis[10] defining a 5-year cutoff point and assessing mortality in the first 5 years and in subsequent years, and *b)* a parametric survival model using functions allowing for nonconstant risks over time (restricted cubic splines), which compares mean survival between the 2 groups at censored and predefined follow-up times (in this study: 5, 8, and 10 years). These approaches permit assessment of the variability of the effect of the intervention over time and recognition that the effect may change during follow-up.

Landmark analysis is based on the change at the time of follow-up initiation. Two initiation points are defined: at the time of the intervention and 5 years later. Although the method allows a comparison of median survival at both follow-up periods, it does not estimate the effect of the intervention at different time points or assess how that effect changes over time. Limitations include the arbitrary selection of the cutoff point or the loss of the randomization effect, with the possible presence of confounding variables in the survivor groups in the second period.[11] This landmark strategy has also been used in other types of studies to differentiate responders from nonresponders and to identify time-varying variables or states, such as patients being placed on the heart transplant waiting list and the time at which transplantation is performed.

Survival models allowing for nonconstant risks estimate the magnitude of the effect over a defined time. In this study, both approaches yielded similar results, supporting the consistency of the findings.

From the clinical perspective, the guidelines of the American Heart Association and the European Society of Cardiology recommend PCI as an alternative to coronary artery bypass surgery in patients with left main coronary artery lesions or complex multivessel lesions. However, this recommendation is based on studies with a maximum follow-up of 5 years. In a recent meta-analysis of clinical trials with a 5-year follow-up, also performed by Formica et al., [12] patients managed with PCI exhibited higher mortality. Nonetheless, other studies that exclusively included patients with left main coronary artery lesions found no significant differences in mortality between PCI and surgery.[13]

The general improvements in life expectancy raises the question of the long-term impact ($>$ 5 years) of these interventions. Formica et al. concluded that mortality was higher in patients treated with PCI than in those who underwent surgical treatment, particularly in the first 5 years of follow-up. This longer survival in patients who underwent surgery translated into a life expectancy increase of 2.4 months. Recently, Feng et al. found no significant differences between surgery and PCI in another meta-analysis of the differences in mortality beyond 5 years.[14] On the one hand, this meta-analysis included 2 small studies ($n < 110$) and 1 medium-sized study[15] that were not considered by Formica et al., and, in addition, data were not included from the FREEDOM-2019 [16] and BEST-2022 [17] studies. This difference in the original studies included in these 2 meta-analyses may explain the discrepancies in the results and also serves to highlight the importance of the search and inclusion/exclusion criteria in meta-analyses.

A crucial limitation identified by the authors is the variability in the percutaneous revascularization methods used in the studies. These methods could also differ from current practices, because the patients included in the studies constituting this meta-analysis were selected between 2004 and 2013. Current evidence indicates greater effectiveness of surgery over PCI in reducing mortality in patients with complex coronary lesions. Nonetheless, the question remains whether this greater effectiveness of surgery is maintained in patients with left main coronary artery lesions,[13] as well as concerning the effectiveness of the new PCI methods.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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